Sheet 1 of 7 Form 1449* Atty. Docket No.: 735.034US2 Serial No. 09/117,558 Applicant: Edmond J. LaVoie et al. INFORMATION DISCLOSURE STATEMENT BY APPLICANT Filing Date: July 31, 1998 Group: 1612 veral sheets if necessary) U.S. PATENT DOCUMENTS Filing Date Class Subclass If Appropriate Date 11/28/65 26,065 07/19/1966 Marvel, C.S., et al. .260 47 02/09/56 2,985,661 05/23/1961 Hien, D.W., et al. 260 309 Guglielmetti, L., et al.260 240 08/16/65 3,449,330 06/10/1969 03/23/67 3,538,097 11/03/1970 Lowe, H., et al. 260 268 3,912,740 10/14/1975 Zee-Chang, K., et al. 260 286 02/28/74 07/03/1990 Borch, R.F., et al. 424 10 09/12/88 4,938,949 395 03/26/90 _ 5,106,863 04/21/1992 Hajos, Z.G., et al. 514 291 01/24/91 5,126,351 06/30/1992 Luzzio, M.J., et al. 514 09/14/1993 Wall, M.E., et al. 279 10/22/90 5,244,903 514 Luzzi, M.J., et al. 279 08/18/92 06/07/1994 514 5,318,976 03/20/96 06/16/1998 La Voie, E.J., et al. 514 394 5,767,142 01/21/97 LaVoie, E.J., et al. 514 394 5,770,617 06/23/1998 05/17/95 5,807,874 338 09/15/1998 LaVoie, E.J., et al. 514 FOREIGN PATENT DOCUMENTS **Examiner Translation Subclass Initial Document Number Country Class Yes | 07/29/1992 C07D 491/056 0496634 ---European ᢍᢋ C07D 235/20 with Abstract 1530628___ 12/23/1989 Russia C07D 2108955 ---05/25/1983 Great Britain 491/00 PCT C07D 221/18 92/21661,---12/10/1992 C07D 235/18 11/21/1996 96/36612 ∽ PCT 08/14/1997 CO7D 455/02 97/29106 PCT 98/12181~ 03/26/1998 C07D 221/18 PCT 235/18 07/23/1998 C07D 98/31673 PCT OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) **Ryaminer Aguirre, J.M., et al., "Reaction of 1,2-diarylethylamides with Ethyl Polyphosphate (EPP): Correlation of the von Braun, Ritter and Bischler-Napieralski Reactions", Chemical Abstracts, Vol. 111, No. 13., Abstract No. 115004, 646, (September 25, 1989). "Synthesis of 7,8-Benzophenanthridines", Indian Journal Arumugam, N., et al., of Chemistry, Vol. 12, 664-667, (July 1974) & "Silicon-Mediated Isoquinoline Synthesis: Preparation and Badia, D., et al., Stereochemical Characterization of 4-hydroxy-3-phenylisoquinolines", <u>Chemical</u> <u>Abstract No. 131034</u>, (September 28, 1992) Abstracts, vol. 117, No. 13, Examiner Date Considered 20 October 1999

^{**}EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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| BY APPLICANT E (Go several sheets if necessary) | Filing Date: July 31, 1998 | Group: 1612 |
| OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) Bradsher, C.K., et al., "\alpha-Acyl-o-tolunitriles as Intermediates in the Preparation of 3-substituted Isoquinolines and 1-amino-2-benzopyrylium | | |
| Derivatives", Chemical Ab | stracts, Vol. 89, No. 21, A | <u>bstract No. 179810</u> , 590, |
| 33342: Cytoxicity and Dru | ew Mammalian DNA Topoisomer g Resistance in Human Cell , 1332-1337, (March 15, 19 | Cultures", <u>Cancer</u> |
| | Minor Groove-Binding Ligan se I Inhibitors", Proc. Nat | |

"DNA Topoisomerases: Essential Enzymes and Lethal Çhen, A.Y., et al., Targets", Annu. Rev. Pharmacol. Toxicol., Vol. 34, 191-218, (1994) . "N-(5,5-Diacetoxypent-l-yl)doxorubicin: A New Intensely Cherif, A., et al., Potent Doxorubicin Analogue", J. Med. Chem., 35, 3208-3214, D'arpa, P., et al., "Topoisomerase-Targeting Antitumor Drugs", Biochimica et Biophysica Acta, 989, 163-177, (1989). Dominguez, E., et al., "Dehydrogenation Reactions of 1-substituted-3-aryltetrahydroisoquin oline derivatives", Chemical Abstracts, Vol. 101, No. 11, Abstract No. 90742, 624, (1984), Dorofeenko, G.N., et al., "Synthesis of 3-aryl Derivatives of 2-benzopyrylium salts with free α -positions", Chemical Abstracts, Vol. 74, No. 15, Abstract No. 76295, 432, (1971). "Reaction of Benzocyclobutene Oxides with Nitriles: Fitzgerald, J.J., et al., Synthesis of Hypecumine and other 3-substituted Isoquinolines", Chemical Abstracts, Vol. 122, No. 7, Abstract No. 081704, 1128, (February 13, 1995) "para-Bromination of Aromatic Amines: Fox, G.J., et al., 4-Bromo-N, N-Dimethyl-3-(Trifluoromethyl) Aniline", Org. Syn., 55, 20-23, (1973).

Fujii, N., et al., "Induction of Mammalian DNA Topoisomerase I-mediated DNA Cleavage and DNA Winding by Bulgarein", <u>Journal of Biological Chemistry</u>, Vol. 268, 13160-13165, (1993).

| Examinor | Date Considered | |
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| *Substitute Disclosure Statement Form (PTO-1449) | 1 10 20 1 | |

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OTHER DOCUMENTS

(Including Author, Title, Date, Pertinent Pages, Etc.)

| mj- | Gallo, R.C., et al., "Studies on the Antitumor Activity, Mechanism of Action, and Cell Cycle Effects of Camptothecin", <u>Journal of the National Cancer Institute, 46,</u> 789-795 (April 1971). |
|----------|---|
| | Gopinath, K.W., et al., "Synthesis of Some 1:2- and 7:8-Benzophenanthridines", <u>Journal of the Chemical Society</u> , 504-509 (1958). |
| <u>-</u> | Garcia, A., et al., "A simple Direct Approach to 1-substituted -3-arylisoquinolines from Deoxybenzoins and Nitriles", Chemical Abstracts, Vol. 110, No. 25, Abstract No. 231407, 622, (June 19, 1989). |
| | Gatto, B., et al., "Identification of Topoisomerase I as the Cyctotoxic Target of the Protoberberine Alkaloid Coralyne", Cancer Res., 56, 2795-2800, (1996). |
| | Giovanella, B.C., et al., "Complete Growth Inhibition of Human Cancer -Xenografts in Nude Mice by Treatment with 20-(S) - Camptothecin", <u>Cancer</u> <u>Research, 51</u> , 3052-3055 (June 1, 1991). |
| | Iwao, M., et al., "A Regiospecific Synthesis of Carbazoles via Consecutive Palladium-Catalyzed Cross-Coupling and Aryne-Mediated Cyclization", Heterocycles, 36, 1483-1488, (1993) |
| | Kessar, S.V., et al., "Azasteroids. Part VII. Synthesis of 7-hydroxy-2-methoxy-7,8,9,10-tetrahydrobenzo[i]phenanthridine", <u>J. Chem Soc.</u> , 259-261, (1971) |
| | Kessar, S.V., et al., "New Routes to Condensed Polynuclear Compounds: Part X*-Synthesis of Some Benzo[i]phenanthridines through Benzyne Cyclization", Vol 11, 624-627, (July 1973). |
| | Kim, J.S., et al., "Influence of Steric Factors on Topoisomerase I Inhibition and Cytotoxicity of Bisbenzimidazoles Related to Hoechst 33342", Abstract 4, 86th Annual Meeting of the American Association for Cancer Research, Toronto, Ontario, Canada, 2689, (1995) |
| ant- | Kim, J.S., et al., "Influence of Steric Factors on Topoisomerase I Inhibition and Cytotoxicity of Bisbenzimidazoles Related to Hoechst 33342", Abstract 7, 3rd Annual Scientific Retreat, Cancer Institute of New Jersey, Princeton Marriott Forrestal Village, 28, (1995). |

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| *Substitute Disclosure Statement Form (PTO-1449) | |

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| OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.) | | | |
| PATENT & TRADE | | | |
| 5-substituted Terbenz | Quantitative Structure-activit imidazoles as Topoisomerase I Chem., 6 (2), 163-172, (199 | Poisons and Antitumor | |
| Inhibition and Cytoto | Kim, J.S., et al., "Steric Factors Associated with the Topoisomerase I Inhibition and Cytotoxicity of Substituted Bisbenzimidazoles", Abstract 10. American Assn of Pharmaceutical Scientists, Eastern Regional Meeting, 27, | | |
| Kim, J.S., et al., "S Related Heterocycles a 621-630, (1996) | Structure-activity Relationshias Topoisomerase I Poisons", F | ips of Benzimidazoles and Bioorganic & Med. Chem., 4, | |
| | Kim, J.S., et al., "Substituted 2,5'-Bi-1H-benzimidazoles: Topoisomerase I Inhibition and Cytotoxicity", <u>J. Med. Chem.</u> , Vol. 39, 992-998, (1996) | | |
| | Kitamura, T., et al., "Isoquinoline Derivatives from the Ritter-type Reaction of Vinyl Cations", Chemical Abstracts, Vol. 102, No. 1, Abstract No.6157, (January 7, 1985) | | |
| Groove-binding Ligands 1. 85th Annual Meeting | LaVoie, E.J., et al., "Structure-activity Studies related to Minor Groove-binding Ligands which Inhibit Mammalian DNA Topoisomerase I", Abstract 1, 85th Annual Meeting of American Association for Cancer Research, San Francisco, CA, 2699, (1994) | | |
| | Makhey, D., et al., "Protoberberine Alkaloids and Related Compounds as Dual Inhibitors of Mammalian Topoisomerase I and II", Med Chem. Res., Vol. 5, 1-12, (1994) | | |
| Isoindolo[1,2-b]quina | Meegalla, S.K., et al., "Synthesis and Pharmacological Evaluation of Isoindolo[1,2-b]quinazolinone and Isoindolo[2,1-a]benzimidazole Derivatives Related to the Antitumor Agent Batracylin", J. Med. Chem., 37, 3434-3439, (1994) | | |
| 5,6,13,13a-tetrahydro | Memetzidis, G., et al., "Structure-affinity Relationships of Berbines or 5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizines at α-adrenoceptors", Eur. J. Med. Chem, Vol. 26(6), 605-611, (1991) | | |
| Nelson, J.T., et al., "Proton and Carbon-13 NMR Spectra of Fifteen Substituted Isoquinolines", Chemical Abstracts, Vol. 115, No. 5, Abstract No. 48721, (August 5, 1991) | | | |
| | | | |
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| *Substitute Dischosure Statement Form (PTO-1449) | | | |

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OTHER DOCUMENTS

(Including Author, Title, Date, Pertinent Pages, Etc.)

| my | f | _ | Peters, D., et al., "Synthesis of Various 5-Substituted Uracils", J. Heterocyclic Chem., 27, 2165-2173, (November December 1990). |
|----|---|---|---|
| | | 9 | Pilch, D.S., et al., "Biophysical Characterization of a Cytotoxic, Topoisomerase I Poison", <u>Abstract 8, 3rd Annual Scientific Retreat, Cancer</u> Institute of New Jersey, 3, (1995), |
| | | ţ | Pilch, D.S., et al., "Characterizing the DNA Binding Modes of a Topoisomerase I-poisoning Terbenzimidazole: Evidence for both Intercalative and Minor Groove Binding Properties", <u>Drug Design and Discovery</u> , Vol. 13, 115-133, (1996). |
| | | \ | Piper, J.R., et al., "Synthesis and Antifolate Activity of 5-Methyl-5,10-dideaza Analogues of Aminopterin and Folic Acid and an Alternative Synthesis of 5,10-Dideazatetrahydrofolic Acid, a Potent Inhibitor of Glycinamide Ribonucleotide Formyltransferase", J. Med. Chem., 31, 2164-2169, (1988). |
| | | 1 | Porai-Koshits, B.A., et al., "Imidazole Derivatives. VI. Synthesis of some Polybenzimidazoles", <u>J. Gen. Chem. USSR, 23, as related in Chemical Abstracts, Vol. 48, No. 2, Col. 12740</u> Nov. 10, 1954- |
| | | 1 | Porai-Koshits, B.A., et al., "Imidazole Derivatives. VI. Synthesis of some Polybenzimidazoles", Zhur. Obshchei Khim, 23, as related from Chemical Abstracts, Vol. 48, Col. 4523, April 25, 1954. |
| | |) | Quast, U., et al., "Heterocyclic α -carbinolamines with the Isoquinuclidine Skeleton. 3. Benzoisoquinuclidines", Chemical Abstracts, Vol. 97, No. 21, Abstract No. 182180, 806, (1982). |
| | | 1 | Safaryan, G.P., et al., "2-Benzopyrylium Salts. 25. Reaction of 2-benzopyrylium Salts with some Nucleophiles", Chemical Abstracts, Vol. 96, No. 17, Abstract No. 142656, 736, (1982). |
| .; | | | Schiess, P., et al., "Thermolytic Ring Opening of Acyloxybenzocyclobutenes: an Efficient Route to 3-substituted Isoquinolines", <u>Chemical Abstracts, Vol.</u> 104, No. 19, Abstract No. 168332, 639, (May 12, 1986). |
| m | / | | Shcherbakova, I.V., et al., "2-Benzopyrilium salts. 35. Synthesis of the Natural Alkaloid Dehydronorcoralydine and other Substituted Salts of Dibenzo[a,g]quinolizine", Chemical Abstracts, Vol. 112, No. 19, Abstract No. 179554, 823, (May 7, 1990). |

Examiner Date Considered

*Substitute Distrourer Statement Form (PTO-1449)

^{**}EXAMINER: Initial if citation considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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| PATENT & TRADE | | | |
| Topoisomerase Inhibitory | nthesis and Sequence-Specific Analog of Hoechst 33258 Design em. Res. Toxicol., 5, 597-607, | ed for Altered Base and | |
| 3-aryltetrahydro- and 3,4 | Oxidation Reactions of 2'-func -dihydroisoquinolines", <u>Chemic</u> 854, 1227, (March 11, 1996), | | |
| Related to Hoechst 33342" | Sun, Q., et al., "Structure Activity of Novel Topoisomerase I Inhibitors Related to Hoechst 33342", Abstract 6, American Assn. of Pharmaceutical Scientists, Eastern Regional Meeting, 25, (1995). | | |
| Sun, Q., et al., "Structu Hoechst 33342", Bioorganic (1994). | Sun, Q., et al., "Structure Activity of Topoisomerase I Poisons Related to Hoechst 33342", Bioorganic & Medicinal Chemistry Letters, Vol. 4, 2871-2876, (1994). | | |
| Sun, Q., et al., "Structure-activity Studies Related to Minor Groove-Binding Ligands which Inhibit Mammalian DNA Topoisomerase I", Cancer Institute of New Jersey, First Annual Scientific Retreat, June 7, 1994, Princeton Marriott Forrestal Village, Princeton, New Jersey, 66, (1994), | | | |
| | Sun, Q., et al., "Synthesis and Evaluation of Terbenzimidazoles as Topoisomerase I Inhibitors", Chemical Abstracts, 123(15), Abstract No. 198740, 1241, (1995), | | |
| Novel DNA Topoisomerase I | Sun, Q., et al., "Synthesis and Pharmacological Evaluation of a Series of Novel DNA Topoisomerase I Inhibitors as Antitumor Agents", 86th Annual meeting of the American Association for Cancer Research, Toronto, Ontario, Canada, 2688, (1995), | | |
| Novel DNA Topoisomerase I | Sun, Q., et al., "Synthesis and Pharmacological Evaluation of a Series of Novel DNA Topoisomerase I Inhibitors as Antitumor Agents", Abstract 5, 3rd Annual Scientific Retreat, Cancer Institute of New Jersey, 27, (1995). | | |
| | Sun, Q., et al., "Synthesis of Benzimidazo[2,1-a]isoquinolines and 5,6-Dihydrobenzimidazo[2,1-a]isoquinolines", Syn. Lett., submitted, (1995). | | |
| Walterova, D., et al., "Isolation, Chemistry and Biology of Alkaloids from Plants of Papaveraceae. Part XCV. Practical Application of Isotachophoresis in Analysis of Isoquinoline Alkaloids", Chemical Abstract, Vol. 104, No. 12, Abstract No. 95573, 454 (1986), | | | |
| | | - 1 | |
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| *Substitute DiscWosure Statement Form (PTO-1449) | | | |

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| O 111 3 0 1993 E | OTHER DOCUMENTS Author, Title, Date, Pertinent Pages, Etc.) | | |
| PATENT & TRADE | | | |
| Yadagiri, B., et al., "Convenient Routes to Substituted Benzimidazoles and Imidazolo[4,5-b] Pyridines Using Nitrobenzene as Oxidant", Synthetic Communications, 20(7), 955-963, (1990). | | | |
| Yamamoto, Y., et al., "Reaction of 6H-1, 3-oxazin-6-one with Benzyne Giving Isoquinoline derivatives", Chemical Abstracts, Vol. 118, No. 7, Abstract No. 59563, (February 15, 1993). | | | |
| | Induction of Mammalian DNA Top Saintopin, a New Antitumor Age 838-5845, (1991) | | |
| - NJ 1 | Induction of Mammalian DNA Top Indolocarbazole Derivatives", | | |

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